

| Figure 2A | Two-way ANOVA followed by Bonferroni's multiple comparisons test | | | | | | | | |
|---|--|-----------------------|--------------------------|--------------------------|--------------------|-----------|---------------|-----------|-------------------|
| Two-way RM ANOVA | Matching: Stacked | | | | | | | | |
| Assume sphericity? | Yes | | | | | | | | |
| Alpha | 0,05 | | | | | | | | |
| | | | | | | | | | |
| Source of Variation | % of total variation | P value | P value summary | Significant? | | | | | |
| Interaction | 21.96 | <0.0001 | **** | Yes | | | | | |
| test time | 7.639 | <0.0001 | **** | Yes | | | | | |
| treatment-group | 35.13 | <0.0001 | **** | Yes | | | | | |
| Subject | 20.54 | 0.0219 | * | Yes | | | | | |
| | | | | | | | | | |
| ANOVA table | SS | DF | MS | F (DFn, DFd) | P value | | | | |
| Interaction | 0.5906 | 3 | 0.1969 | F (3, 36) = 25.40 | P<0.0001 | | | | |
| test time | 0.2054 | 1 | 0.2054 | F (1, 36) = 26.50 | P<0.0001 | | | | |
| treatment-group | 0.9447 | 3 | 0.3149 | F (3, 36) = 20.52 | P<0.0001 | | | | |
| Subject | 0.5523 | 36 | 0.01534 | F (36, 36) = 1.980 | P=0.0219 | | | | |
| Residual | 0.279 | 36 | 0.007751 | | | | | | |
| | | | | | | | | | |
| Test details | Predicted (LS) mean 1 | Predicted (LS) mean 2 | Predicted (LS) mean diff | SE of diff, | N1 | N2 | t | DF | Adjusted P Value |
| | | | | | | | | | |
| baseline | | | | | | | | | |
| Vehicle+Vehicle vs. Reserpine+Vehicle | 0.643 | 0.5628 | 0.08016 | 0.04387 | 12 | 12 | 1.827 | 72 | 0.4308 |
| Vehicle+Vehicle vs. Reserpine+Pregabalin | 0.643 | 0.6016 | 0.0414 | 0.04905 | 12 | 8 | 0.8441 | 72 | >0.9999 |
| Vehicle+Vehicle vs. Reserpine+R-715 | 0.643 | 0.5961 | 0.04691 | 0.04905 | 12 | 8 | 0.9565 | 72 | >0.9999 |
| Reserpine+Vehicle vs. Reserpine+Pregabalin | 0.5628 | 0.6016 | -0.03876 | 0.04905 | 12 | 8 | 0.7903 | 72 | >0.9999 |
| Reserpine+Vehicle vs. Reserpine+R-715 | 0.5628 | 0.5961 | -0.03325 | 0.04905 | 12 | 8 | 0.6778 | 72 | >0.9999 |
| Reserpine+Pregabalin vs. Reserpine+R-715 | 0.6016 | 0.5961 | 0.005514 | 0.05373 | 8 | 8 | 0.1026 | 72 | >0.9999 |
| | | | | | | | | | |
| test | | | | | | | | | |
| Vehicle+Vehicle vs. Reserpine+Vehicle | 0.5783 | 0.1857 | 0.3926 | 0.04387 | 12 | 12 | 8.949 | 72 | <0.0001 |
| Vehicle+Vehicle vs. Reserpine+Pregabalin | 0.5783 | 0.5516 | 0.02674 | 0.04905 | 12 | 8 | 0.5451 | 72 | >0.9999 |
| Vehicle+Vehicle vs. Reserpine+R-715 | 0.5783 | 0.6742 | -0.09591 | 0.04905 | 12 | 8 | 1.955 | 72 | 0.3265 |
| Reserpine+Vehicle vs. Reserpine+Pregabalin | 0.1857 | 0.5516 | -0.3658 | 0.04905 | 12 | 8 | 7.459 | 72 | <0.0001 |
| Reserpine+Vehicle vs. Reserpine+R-715 | 0.1857 | 0.6742 | -0.4885 | 0.04905 | 12 | 8 | 9.959 | 72 | <0.0001 |
| Reserpine+Pregabalin vs. Reserpine+R-715 | 0.5516 | 0.6742 | -0.1226 | 0.05373 | 8 | 8 | 2.283 | 72 | 0.1524 |

| Figure 2A | One-way ANOVA followed by Bonferroni's multiple comparisons test | | | | | | | | |
|---|--|---------------------------|--------------|--------------------------|--------------------|------------|--|--|--|
| Test session | | | | | | | | | |
| | | | | | | | | | |
| ANOVA table | SS | DF | MS | F (DFn, DFd) | P value | | | | |
| Treatment (between columns) | 1,496 | 3 | 0,4988 | F (3, 36) = 29,08 | P<0,0001 | | | | |
| Residual (within columns) | 0,6176 | 36 | 0,01716 | | | | | | |
| Total | 2,114 | 39 | | | | | | | |
| | | | | | | | | | |
| Number of families | 1 | | | | | | | | |
| Number of comparisons per family | 6 | | | | | | | | |
| Alpha | 0,05 | | | | | | | | |
| | | | | | | | | | |
| Bonferroni's multiple comparisons test | Mean Diff, | 95,00% CI of diff, | Significant? | Summary | Adjusted P Value | | | | |
| Vehicle+Vehicle vs. Reserpine+Vehicle | 0,3926 | 0,2433 to 0,5419 | Yes | **** | <0,0001 | A-B | | | |
| Vehicle+Vehicle vs. Reserpine+Pregabalin | 0,02674 | -0,1402 to 0,1937 | No | ns | >0,9999 | A-C | | | |
| Vehicle+Vehicle vs. Reserpine+R-715 | -0,09591 | -0,2628 to 0,07101 | No | ns | 0,7045 | A-D | | | |
| Reserpine+Vehicle vs. Reserpine+Pregabalin | -0,3658 | -0,5327 to -0,1989 | Yes | **** | <0,0001 | B-C | | | |
| Reserpine+Vehicle vs. Reserpine+R-715 | -0,4885 | -0,6554 to -0,3216 | Yes | **** | <0,0001 | B-D | | | |
| Reserpine+Pregabalin vs. Reserpine+R-715 | -0,1226 | -0,3055 to 0,06021 | No | ns | 0,4155 | C-D | | | |

| Test details | Mean 1 | Mean 2 | Mean Diff, | SE of diff, | n1 | n2 | t | DF | |
|---|---------------|---------------|----------------|----------------|-----------|-----------|--------------|-----------|--|
| Vehicle+Vehicle vs. Reserpine+Vehicle | 0,5783 | 0,1857 | 0,3926 | 0,05347 | 12 | 12 | 7,341 | 36 | |
| Vehicle+Vehicle vs. Reserpine+Pregabalin | 0,5783 | 0,5516 | 0,02674 | 0,05979 | 12 | 8 | 0,4472 | 36 | |
| Vehicle+Vehicle vs. Reserpine+R-715 | 0,5783 | 0,6742 | -0,09591 | 0,05979 | 12 | 8 | 1,604 | 36 | |
| Reserpine+Vehicle vs. Reserpine+Pregabalin | 0,1857 | 0,5516 | -0,3658 | 0,05979 | 12 | 8 | 6,119 | 36 | |
| Reserpine+Vehicle vs. Reserpine+R-715 | 0,1857 | 0,6742 | -0,4885 | 0,05979 | 12 | 8 | 8,17 | 36 | |
| Reserpine+Pregabalin vs. Reserpine+R-715 | 0,5516 | 0,6742 | -0,1226 | 0,06549 | 8 | 8 | 1,873 | 36 | |

| Figure 2B | | Two-way ANOVA followed by Bonferroni's multiple comparisons test | | | | | | | |
|---------------------------------------|--|--|-----------------------|---------------------------|---------------------|----------|----|--------|----|
| Two-way RM ANOVA | | Matching: Stacked | | | | | | | |
| Assume sphericity? | | Yes | | | | | | | |
| Alpha | | 0,05 | | | | | | | |
| Source of Variation | | % of total variation | P value | P value summary | Significant? | | | | |
| Interaction | | 23.4 | 0.0002 | *** | Yes | | | | |
| test | | 2.344 | 0.1186 | ns | No | | | | |
| treatment | | 20.35 | <0.0001 | **** | Yes | | | | |
| Subject | | 20.19 | 0.941 | ns | No | | | | |
| ANOVA table | | SS | DF | MS | F (DFn, DFd) | P value | | | |
| Interaction | | 0.8841 | 3 | 0.2947 | F (3, 37) = 8.495 | P=0.0002 | | | |
| test time | | 0.08856 | 1 | 0.08856 | F (1, 37) = 2.553 | P=0.1186 | | | |
| treatment-group | | 0.7688 | 3 | 0.2563 | F (3, 37) = 12.43 | P<0.0001 | | | |
| Subject | | 0.7629 | 37 | 0.02062 | F (37, 37) = 0.5943 | P=0.9410 | | | |
| Residual | | 1.284 | 37 | 0.03469 | | | | | |
| Test details | | Predicted (LS) mean 1 | Predicted (LS) mean 2 | Predicted (LS) mean diff, | SE of diff, | N1 | N2 | t | DF |
| baseline | | | | | | | | | |
| Vehicle+Vehicle vs. Vehicle+KOB1 | | 0.5998 | 0.5727 | 0.02712 | 0.07437 | 10 | 10 | 0.3647 | 74 |
| Vehicle+Vehicle vs. Reserpine+Vehicle | | 0.5998 | 0.6342 | -0.03443 | 0.07437 | 10 | 10 | 0.463 | 74 |
| Vehicle+Vehicle vs. Reserpine+KOB1 | | 0.5998 | 0.6431 | -0.04333 | 0.07266 | 10 | 11 | 0.5964 | 74 |
| Vehicle+KOB1 vs. Reserpine+Vehicle | | 0.5727 | 0.6342 | -0.06156 | 0.07437 | 10 | 10 | 0.8277 | 74 |
| Vehicle+KOB1 vs. Reserpine+KOB1 | | 0.5727 | 0.6431 | -0.07046 | 0.07266 | 10 | 11 | 0.9697 | 74 |
| Reserpine+Vehicle vs. Reserpine+KOB1 | | 0.6342 | 0.6431 | -0.008899 | 0.07266 | 10 | 11 | 0.1225 | 74 |
| test | | | | | | | | | |
| Vehicle+Vehicle vs. Vehicle+KOB1 | | 0.578 | 0.6591 | -0.08112 | 0.07437 | 10 | 10 | 1.091 | 74 |
| Vehicle+Vehicle vs. Reserpine+Vehicle | | 0.578 | 0.2153 | 0.3626 | 0.07437 | 10 | 10 | 4.876 | 74 |
| Vehicle+Vehicle vs. Reserpine+KOB1 | | 0.578 | 0.7343 | -0.1563 | 0.07266 | 10 | 11 | 2.152 | 74 |
| Vehicle+KOB1 vs. Reserpine+Vehicle | | 0.6591 | 0.2153 | 0.4437 | 0.07437 | 10 | 10 | 5.967 | 74 |
| Vehicle+KOB1 vs. Reserpine+KOB1 | | 0.6591 | 0.7343 | -0.07523 | 0.07266 | 10 | 11 | 1.035 | 74 |
| Reserpine+Vehicle vs. Reserpine+KOB1 | | 0.2153 | 0.7343 | -0.519 | 0.07266 | 10 | 11 | 7.142 | 74 |

| Figure 2B | | One-way ANOVA followed by Bonferroni's multiple comparisons test | | | | | | | |
|--|--|--|--------------------|--------------|-------------------|------------------|-----|--|--|
| Test session | | | | | | | | | |
| ANOVA table | | SS | DF | MS | F (DFn, DFd) | P value | | | |
| Treatment (between columns) | | 1.62 | 3 | 0.5401 | F (3, 37) = 20.35 | P<0.0001 | | | |
| Residual (within columns) | | 0.982 | 37 | 0,02654 | | | | | |
| Total | | 2.602 | 40 | | | | | | |
| Number of families | | 1 | | | | | | | |
| Number of comparisons per family | | 6 | | | | | | | |
| Alpha | | 0,05 | | | | | | | |
| Bonferroni's multiple comparisons test | | Mean Diff, | 95,00% CI of diff, | Significant? | Summary | Adjusted P Value | | | |
| Vehicle+Vehicle vs. Vehicle+KOB1 | | -0.08112 | -0.2842 to 0.1220 | No | ns | >0.9999 | A-B | | |
| Vehicle+Vehicle vs. Reserpine+Vehicle | | 0.3626 | 0.1595 to 0.5657 | Yes | **** | <0.0001 | A-C | | |
| Vehicle+Vehicle vs. Reserpine+KOB1 | | -0.1563 | -0.3548 to 0.04208 | No | ns | 0.2064 | A-D | | |
| Vehicle+KOB1 vs. Reserpine+Vehicle | | 0.4437 | 0.2406 to 0.6468 | Yes | **** | <0.0001 | B-C | | |
| Vehicle+KOB1 vs. Reserpine+KOB1 | | -0.07523 | -0.2737 to 0.1232 | No | ns | >0.9999 | B-D | | |
| Reserpine+Vehicle vs. Reserpine+KOB1 | | -0.519 | -0.7174 to -0.3205 | Yes | **** | <0.0001 | C-D | | |

| Test details | Mean 1 | Mean 2 | Mean Diff. | SE of diff. | n1 | n2 | t | DF | |
|--|---------------|---------------|---------------|----------------|-----------|-----------|--------------|----|--|
| Vehicle+Vehicle vs. Vehicle+KOB1 | 0.578 | 0.6591 | -0.08112 | 0.07286 | 10 | 10 | 1.113 | 37 | |
| Vehicle+Vehicle vs. Reserpine+Vehicle | 0.578 | 0.2153 | 0.3626 | 0.07286 | 10 | 10 | 4.977 | 37 | |
| Vehicle+Vehicle vs. Reserpine+KOB1 | 0.578 | 0.7343 | -0.1563 | 0.07118 | 10 | 11 | 2.196 | 37 | |
| Vehicle+KOB1 vs. Reserpine+Vehicle | 0.6591 | 0.2153 | 0.4437 | 0.07286 | 10 | 10 | 6.09 | 37 | |
| Vehicle+KOB1 vs. Reserpine+KOB1 | 0.6591 | 0.7343 | -0.07523 | 0.07118 | 10 | 11 | 1.057 | 37 | |
| Reserpine+Vehicle vs. Reserpine+KOB1 | 0.2153 | 0.7343 | -0.519 | 0.07118 | 10 | 11 | 7.291 | 37 | |